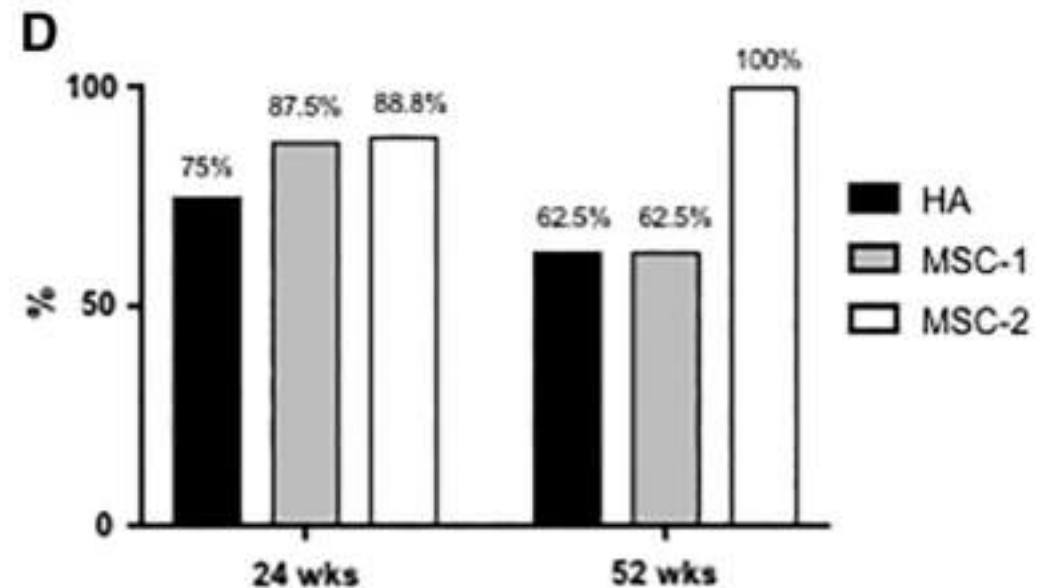
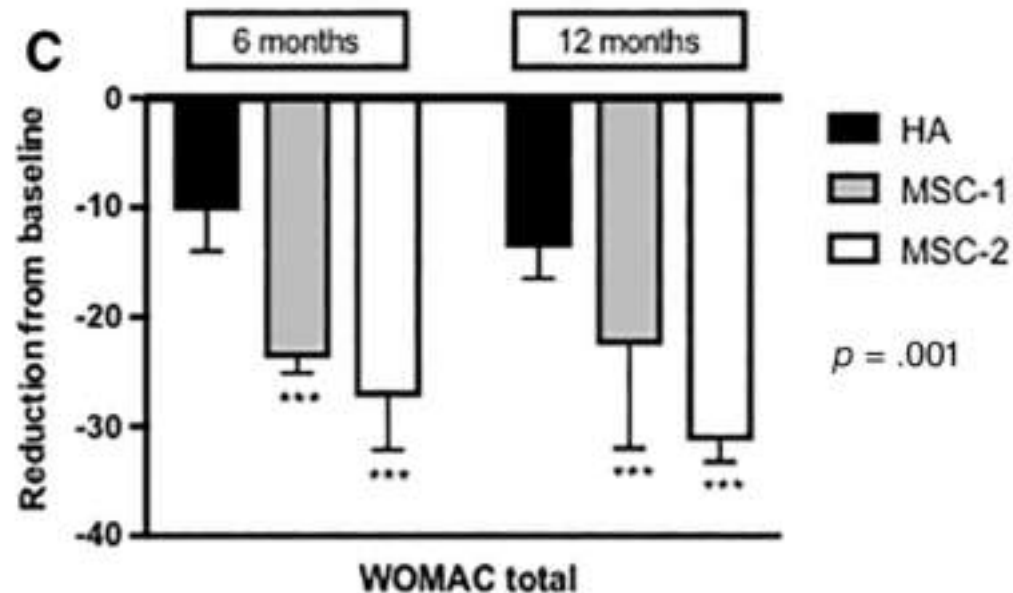


MSC several IA injections

- **One or several injections ?**

- RCT double-blind versus HA
- 3 arms with one-year follow-up
 - HA one injection
 - UC-MSC one injection 20.10^6
 - UC-MSC two injections 20.10^6 and 6-month interval



MSC clinical results in OA



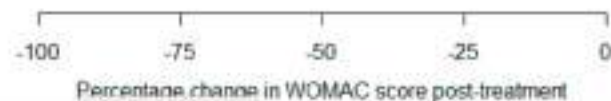
Systematic Review

Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis

Nikhil Agarwal ¹, Christopher Mak ², Christine Bojanic ³, Kendrick To ² and Wasim Khan ^{2,*}

Months Post-Tx	N	% Δ [95% CI]
≤1 month	65	-20.24 [-35.70, -4.78]
2 months	44	-37.69 [-50.30, -25.08]
3 months	103	-41.84 [-53.51, -30.17]
6 months	164	-47.04 [-54.43, -39.65]
12 months	138	-58.44 [-66.41, -50.47]
18 months	25	-65.59 [-79.86, -51.32]
24 months	56	-62.11 [-72.68, -51.54]

RE Model
($Q = 34.33$, $df = 6$, $p < 0.0001$; $I^2 = 86.8\%$)



Recommendations and metaanalyses

Safety and efficacy of adipose-derived mesenchymal stem cells for knee osteoarthritis: A systematic review and m-analysis

Mohamed Gadelkarim ^{a,b,1,*}, Aya Abd Elmegeed ^{c,1}, Ahmed Hafez Allam ^{d,1}, Ahmed K. Awad ^e, Mostafa Ahmed Shehata ^{b,f}, Asmaa AbouEl-Enein ^g, Mohamed Eid Alsadek ^h, Mohammad Abo Deeb ⁱ, Ahmed M. Afifi ^j

Conclusion: In the present single-arm meta-analysis, ADMSCs were associated with significant reduction in pain and improvement in QOL and knee functions in patients with knee OA. However, double arm analyses did not confirm these positive findings, which may be returned to the small sample size of included patients. Therefore, to introduce ADMSCs into clinical practice and establish guidelines for their use, more randomized controlled clinical trials with large sample sizes and long-term follow-ups are needed.

➡ Heterogeneity in the current literature
Risk of bias not negligible

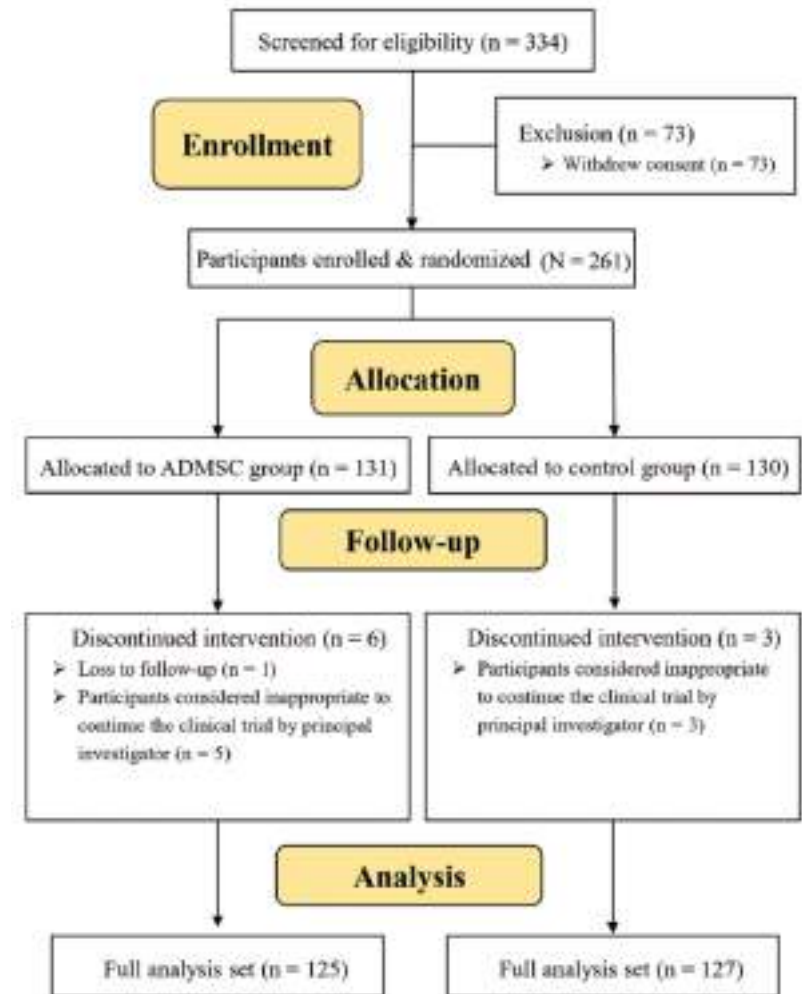
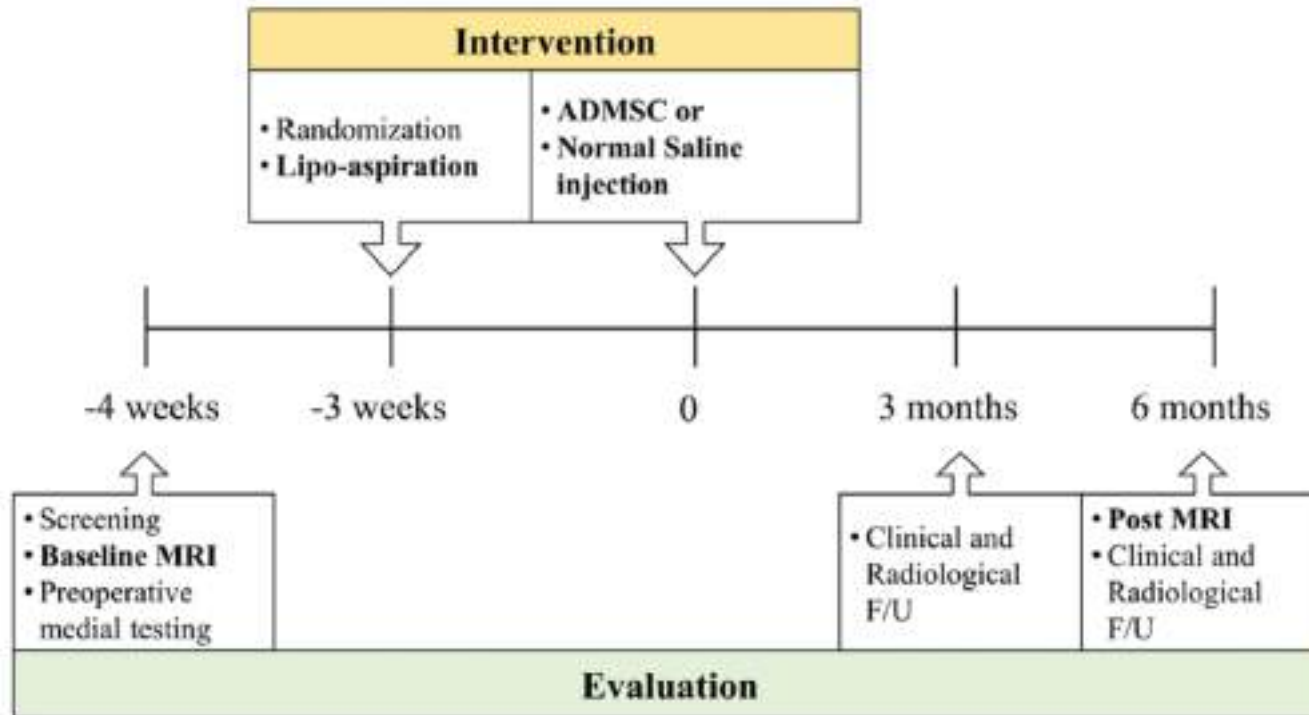
The first (recent) phase III study

Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis

A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial

Kang-II Kim, MD, PhD , Myung Chul Lee, MD, PhD, Ju Hong Lee, MD, PhD, Young-Wan Moon, MD, PhD, Woo-Suk Lee, MD, PhD, Han-Jun Lee, MD, PhD, Sun-Chul Hwang, MD, PhD, Yong In, MD, PhD, Oog-Jin Shon, MD, PhD, Ki-Cheor Bae, MD, PhD, Sang-Jun Song, MD, PhD, and Kwan Kyu Park, MD, PhD
Investigation performed at Kyung Hee University Hospital at Gangdong, Seoul, Korea

The first (recent) phase III study



The first (recent) phase III study

- Eligibility criteria
 - VAS > 50 mm
 - WOMAC total > 40 mm
 - Grade 3 (KL)
- One single i.a injection ADMSC (3mL)
- Dosis : 100×10^6

The first (recent) phase III study

TABLE 1
Demographics and Baseline Characteristics: Full Analysis Set^a

	ADMSC (n = 125)	Control (n = 127)
Age, y	63.7 ± 7.1	63.8 ± 7.1
Sex, male:female, No.	39:86	26:101
Body mass index, kg/m ²	26.3 ± 3.2	25.9 ± 3.1
Smoking, No. (%)	7 (5.6)	5 (3.9)
Duration of osteoarthritis diagnosis, mo	84.1 ± 68.1	85.7 ± 66.5
Symptom duration, mo	113.1 ± 79.1	108.3 ± 84.6
Radiologic data		
K-L grade 1:2:3:4, No.	0:0:125:0	0:0:127:0
HKA angle, deg ^b	-3.8 ± 5.3	-3.3 ± 4.7
Joint space width, mm	3.5 ± 1.3	3.6 ± 1.5
Clinical data		
100-mm VAS for pain	57.7 ± 17.1	60.9 ± 16.6
WOMAC index		
Pain	10.7 ± 3.3	11.3 ± 3.2
Stiffness	4.5 ± 1.3	4.9 ± 1.5
Function	39.8 ± 9.4	41.8 ± 10.3
Total	55.0 ± 13.4	58.0 ± 14.4
KOOS		
Symptoms	55.7 ± 15.9	51.7 ± 15.9
Pain	50.1 ± 13.9	46.9 ± 16.2
Activities of Daily Living	53.7 ± 14.8	50.2 ± 17.0
Sport and Recreation	23.6 ± 18.3	21.5 ± 19.0
Quality of Life	32.9 ± 14.3	31.8 ± 16.1
SF-36		
PCS	38.0 ± 5.9	37.9 ± 6.2
MCS	46.6 ± 10.1	45.9 ± 9.6
IKDC subjective score	38.5 ± 11.7	37.0 ± 13.1

The first (recent) phase III study

TABLE 2
Mean Improvements in Primary Outcomes From Baseline to the Follow-up Visits: Full Analysis Set^a

Outcome: LMM ^b or Time	ADMSC (n = 125) ^c	Control (n = 127) ^c	95% CI of the Difference	P Value
Δ 100-mm VAS on pain				
LMM	11.8 (2.9) ^b		6.4-17.4	<.001
3 months	22.2 ± 24.6	13.2 ± 23.7	0.6-12.7	.030
6 months	25.2 ± 24.6	15.5 ± 23.7	3.0-15.3	.004
Δ WOMAC				
Δ Pain subscore				
LMM	2.0 (0.5) ^b		1.0-3.0	<.001
3 months	3.8 ± 4.1	2.7 ± 3.8	0.1-2.1	.027
6 months	4.3 ± 4.0	2.7 ± 4.4	0.6-2.7	.003
Δ Stiffness subscore				
LMM	0.8 (0.2) ^b		0.3-1.2	<.001
3 months	1.4 ± 1.8	1.3 ± 1.6	-0.3-0.5	.620
6 months	1.8 ± 1.9	1.3 ± 1.9	0.1-1.0	.017
Δ Function subscore				
LMM	6.1 (1.7) ^b		2.8-9.4	<.001
3 months	13.3 ± 13.6	9.7 ± 12.1	0.4-6.8	.030
6 months	15.7 ± 13.4	10.3 ± 14.1	2.0-8.9	.002
Δ Total score				
LMM	8.9 (2.3) ^b		4.3-13.4	<.001
3 months	19.1 ± 18.7	13.5 ± 17.2	0.35-9.2	.024
6 months	21.7 ± 18.6	14.3 ± 19.2	2.8-12.4	.002

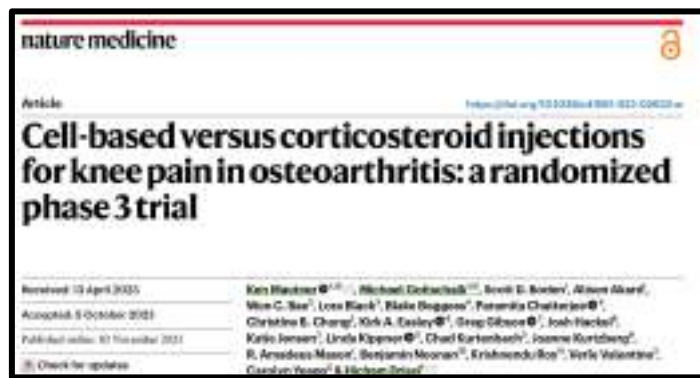
The first (recent) phase III study

TABLE 4
Treatment-Emergent Adverse Events in the Safety Set^a

	ADMSC (n = 125)	Control (n = 127)	P Value
Patient summary			
Patients with TEAE	48 (38.4)	41 (32.3)	.310
Patients with SAE	1 (0.8)	3 (2.4)	.622
Patients with fatal SAE	0	0	>.999
Procedure-related joint pain	3 (2.4)	1 (0.8)	.337
Procedure-related joint swelling	3 (2.4)	0	.198
Event summary			
Total TEAEs	72	65	
Severity by NCI-CTCAE scale			
Grade 1	50	36	
Grade 2	22	29	
Grade 3	0	0	
Grade 4	0	0	
Grade 5	0	0	
Relationship between the treatment and TEAEs			
Certain	0	0	
Probable/likely	8	2	
Possible	17	2	
Unlikely	42	58	
Conditional/unclassified	3	0	
Unassessable/unclassifiable	1	0	
Not applicable	1	3	
Result of TEAEs			
Recovered/resolved	54	43	
Recovering/resolving	16	21	
Not recovered/not resolved	2	1	
Recovered or resolved with sequelae	0	0	
Death	0	0	
Unknown	0	0	

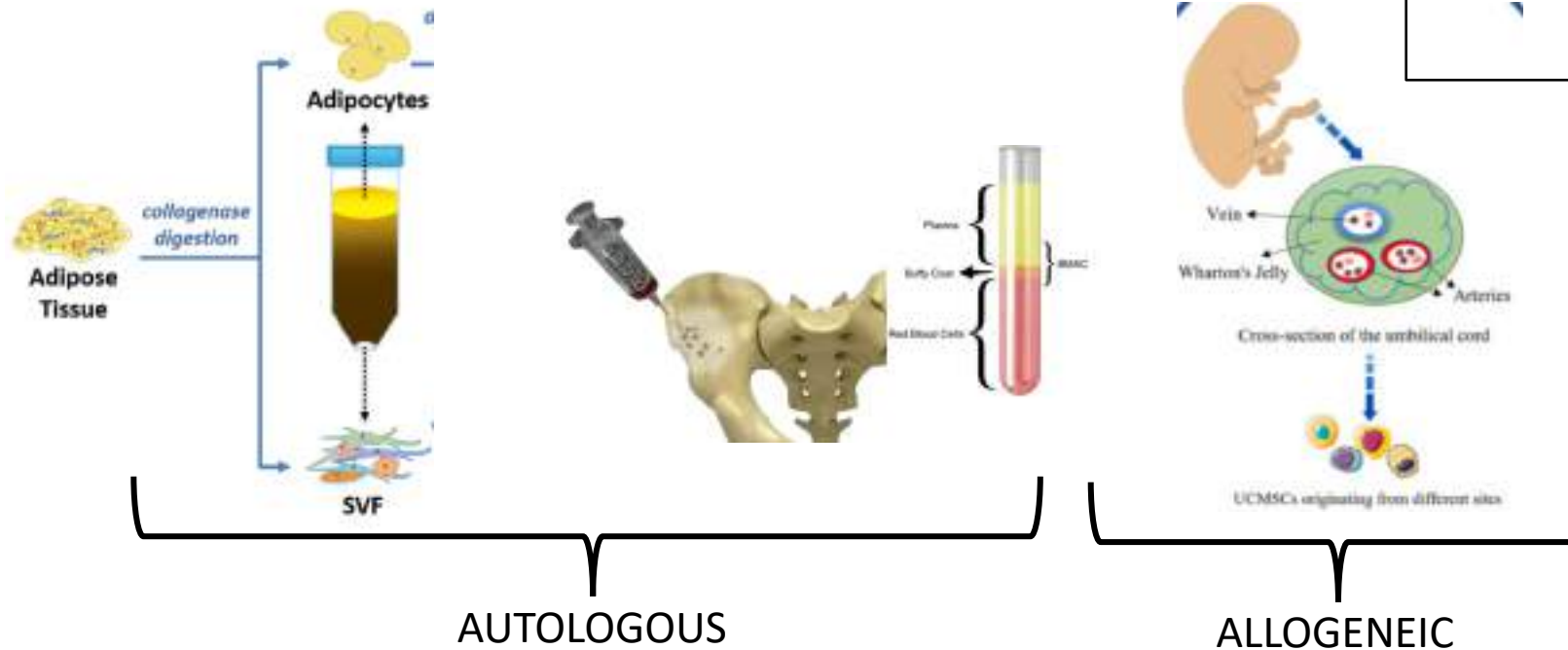


- > Global MSC Market Size = USD 1,715 Million in 2021
- > Cell-based therapies positive ??? small sample sizes and high risk of bias



- > Global MSC Market Size = USD 1,715 Million in 2021
- > Cell-based therapies positive ??? small sample sizes and high risk of bias

One single i.a. injection (7 mL)
3 interventions arms
One comparator : steroid
Single-blind study +++



Release Criteria	SVF	BMAC	UCT
Total Nucleated Cell Count	>5 million cells (no maximum cell count)	>200 million cells but <2 billion cells	>10 million cells but < 20 million cells
Cell Viability	≥70%	≥70%	≥70%
Endotoxin Testing	<20 EU total	< 350 EU total	Not required at point of care

Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial

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Check for updates

Karl Mautner^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,122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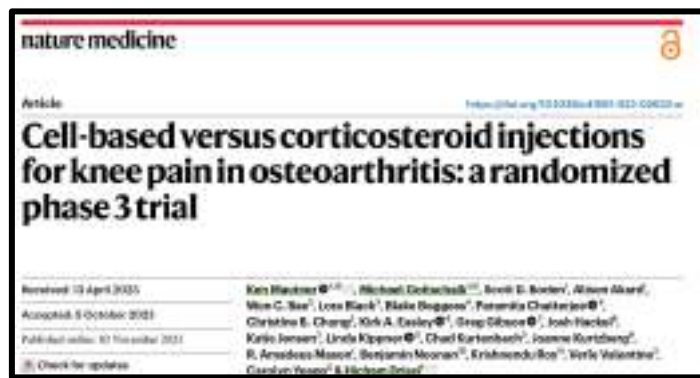
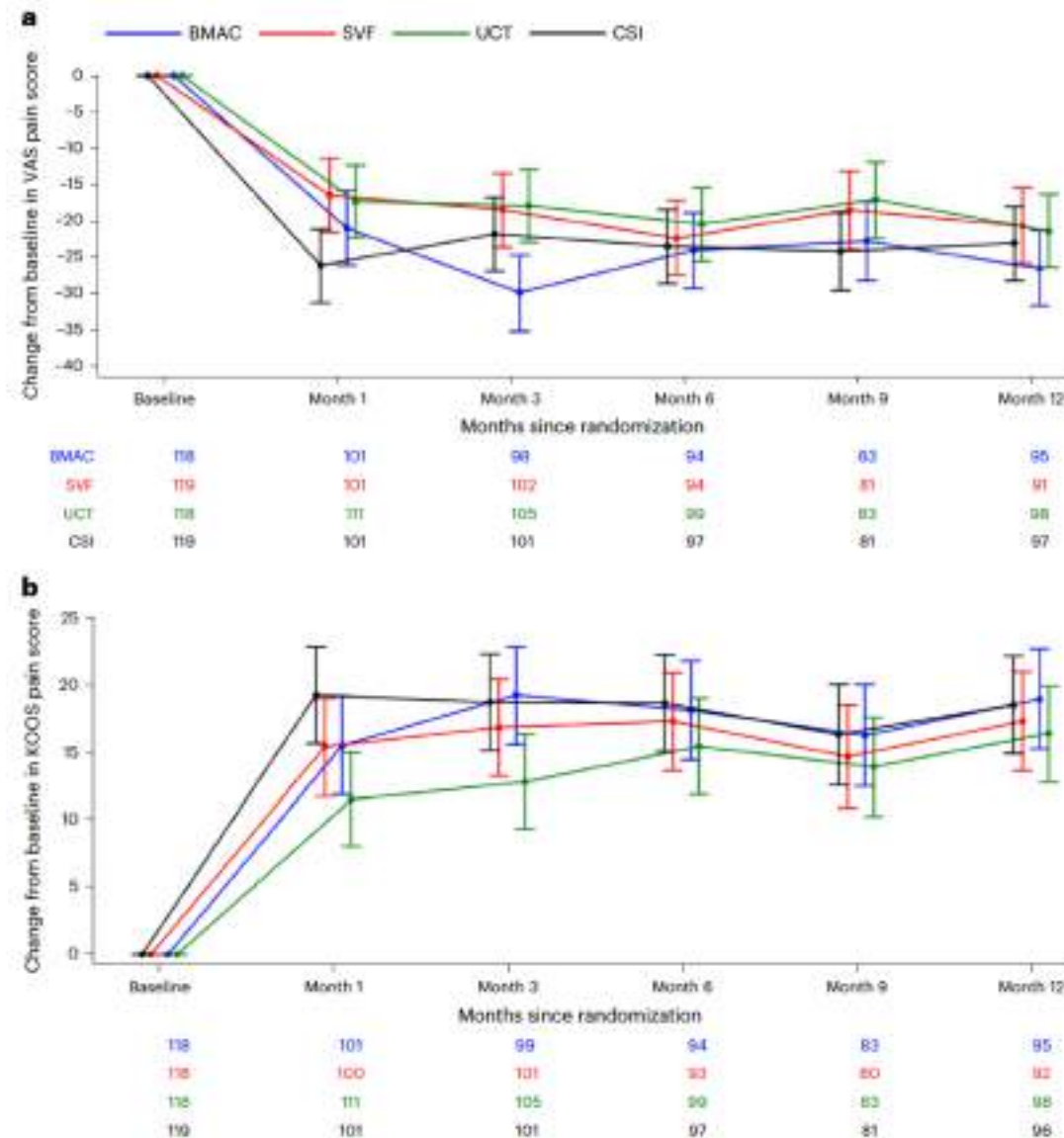


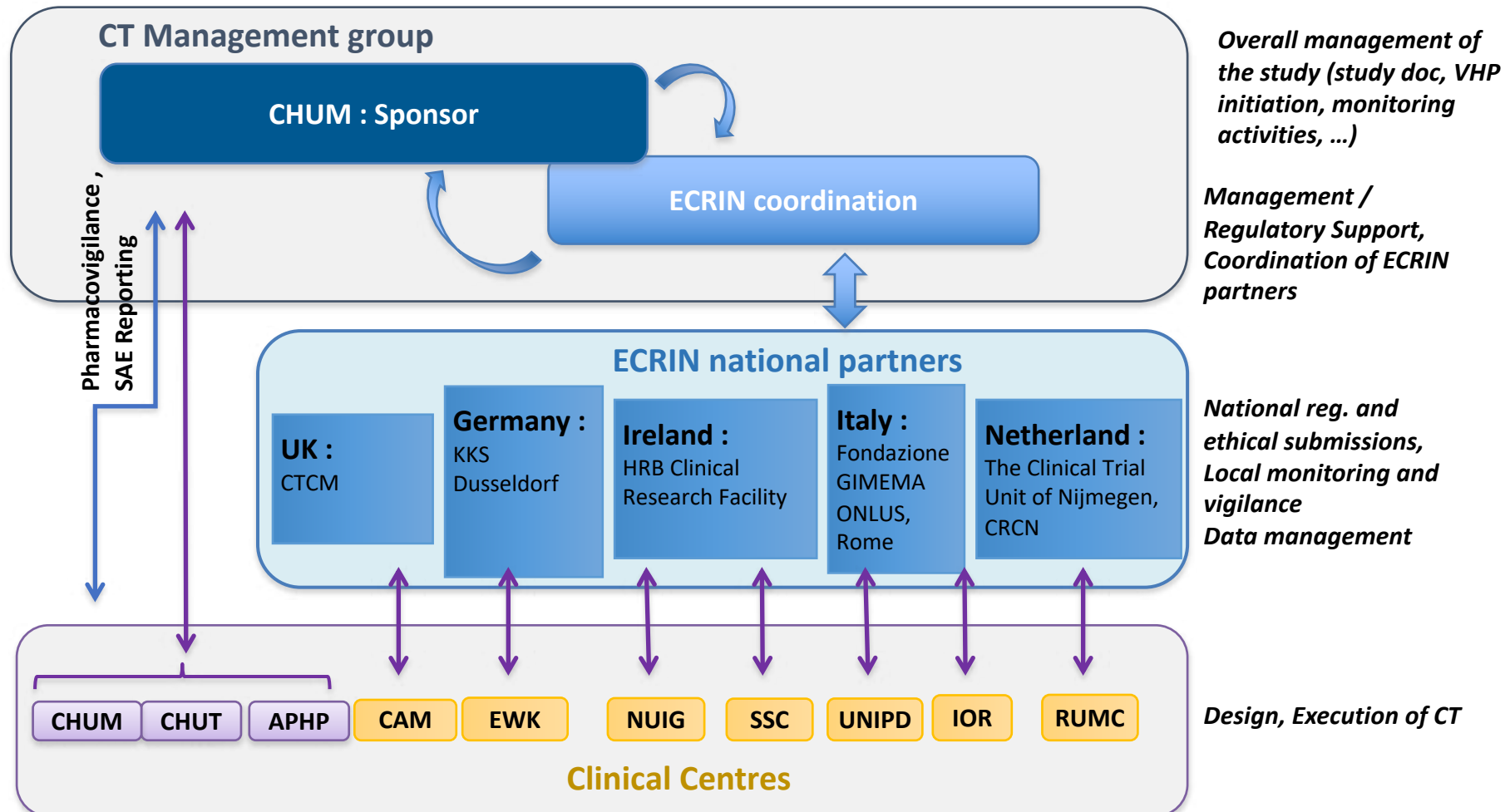
Table 1 | Demographic and baseline characteristics by treatment group for the intent-to-treat population

	BMAC <i>n</i> =118	SVF <i>n</i> =119	UCT <i>n</i> =118	CSI <i>n</i> =120	All subjects <i>n</i> =475
Age (years)					
Mean±s.d.	58.6±7.3	58.2±7.3	57.9±8.2	58.3±8.1	58.3±7.7
≥60, <i>n</i> (%)	61 (52%)	56 (47%)	54 (46%)	58 (48%)	229 (48%)
<60, <i>n</i> (%)	57 (48%)	63 (53%)	64 (54%)	62 (52%)	246 (52%)
BMI (kg m ⁻²), <i>n</i>					
Mean±s.d.	30.6±6.0	30.5±6.4	30.9±5.4	31.2±6.2	30.8±6.0
KL grade, <i>n</i> (%)					
Grade 2	31 (26%)	34 (29%)	44 (37%)	34 (28%)	143 (30%)
Grade 3	43 (36%)	52 (44%)	42 (36%)	54 (45%)	191 (40%)
Grade 4	44 (37%)	33 (28%)	32 (27%)	32 (27%)	141 (30%)
Male, <i>n</i> (%)	56 (48%)	56 (47%)	53 (45%)	49 (41%)	214 (45%)
Female, <i>n</i> (%)	62 (53%)	63 (53%)	65 (55%)	71 (59%)	261 (55%)



- > Cell-based therapy failed to demonstrate superiority over i.a. steroid
- > No subgroup differences
- > Good safety profiles (joint swelling, hematoma)

ADIPOA 2 clinical study



Chronic low back pain

- La lombalgie est la principale cause d'invalidité dans la population adulte en France et dans le reste du monde
- La discopathie dégénérative (DDD) est la principale cause de lombalgie chronique (>40%)

Traitements Actuels:

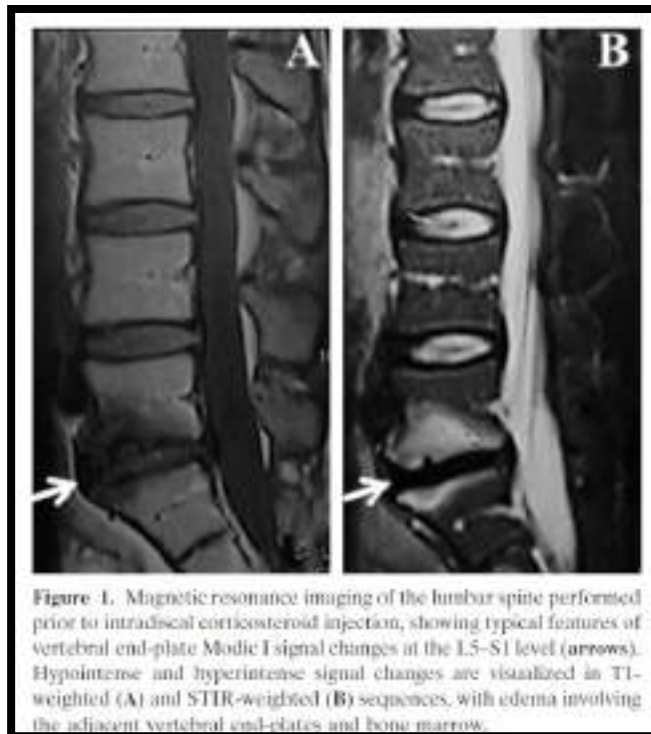
Tt médicaux: analgésiques, anti-inflammatoires, orthèses lombaires rigides

Tt chirurgicaux : arthrodèse, prothèses discales

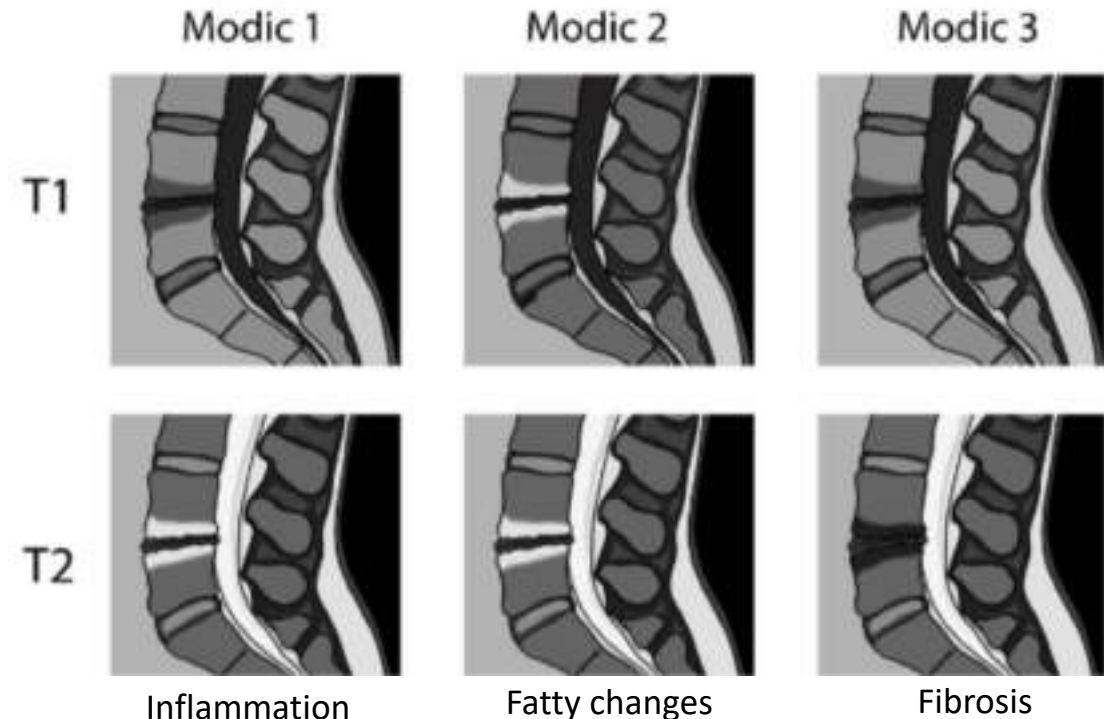
Injections intra-discales de stéroïdes (pas d'effet à moyen ou long terme)

Chronic low back pain

- La discopathie active (MODIC 1)
 - 5-40% des lombalgies
 - Rare dans la population asymptomatique
 - Associée à la réussite de la chirurgie
 - hypoT1 / hyperT2
 - Inflammation locale +++

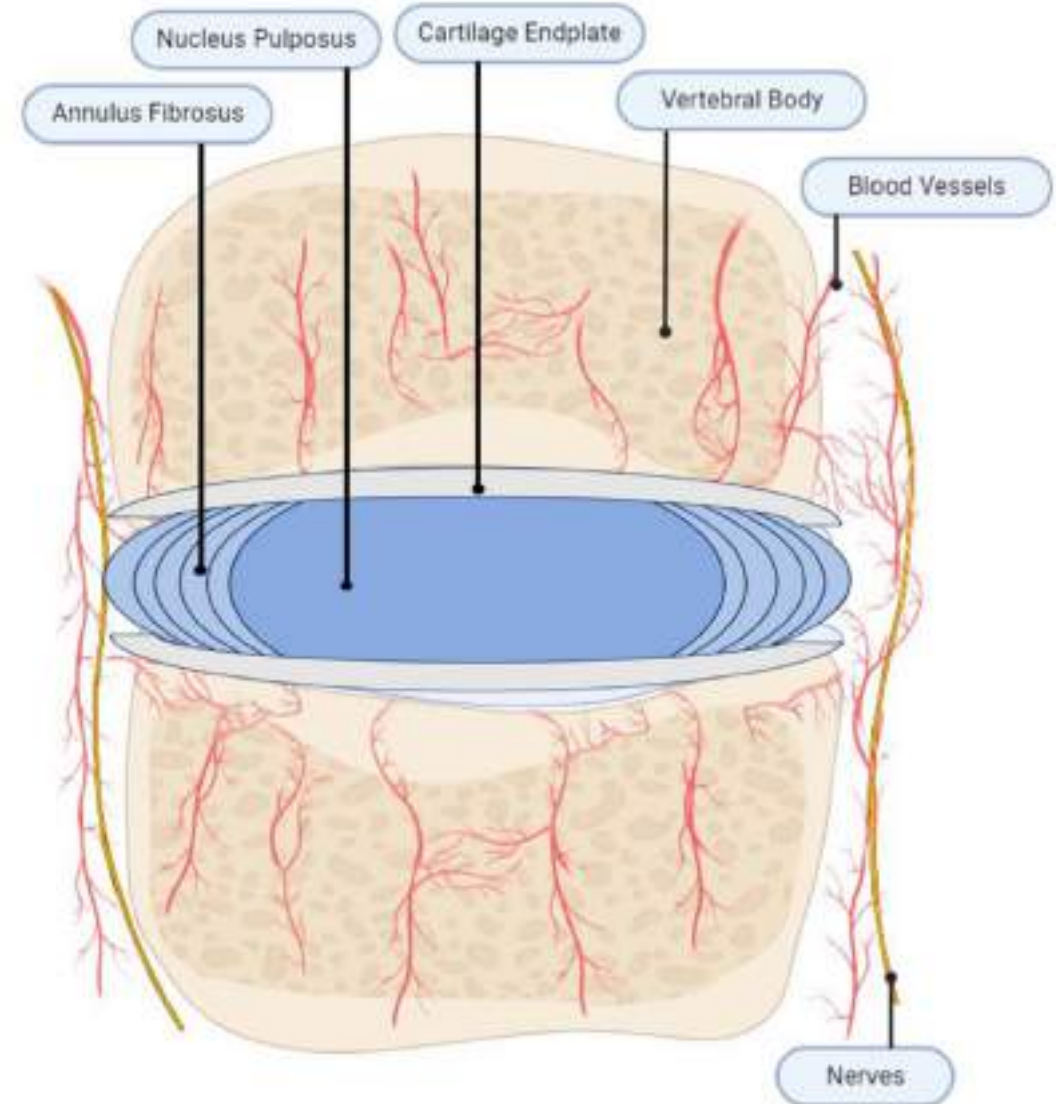


Classification de Modic



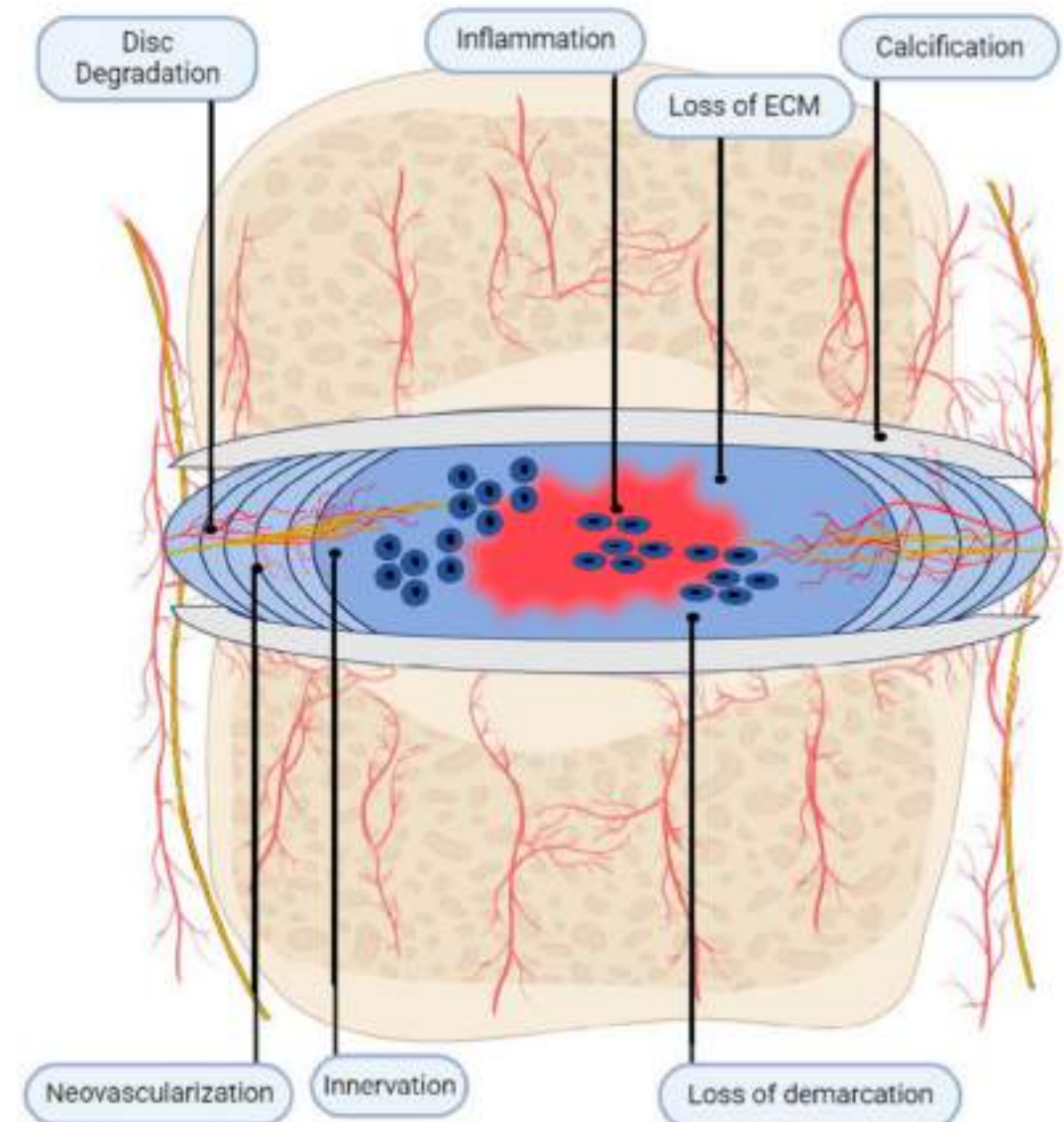
Physiologie du disque IV

- Matrice extra-cellulaire
 - Collagène, PG et eau : 95%
 - Collagène = armature fibreuse
 - Concentration diminue de la périphérie vers le centre
 - Changements des fibres de collagène
 - PG = assurent pression osmotique
 - Equilibre entre :
 - Catabolisme : MMPs, IL1, TNF, ADAM
 - Anabolisme : BMP2, BMP7, GDF5, TGFb, IGF1



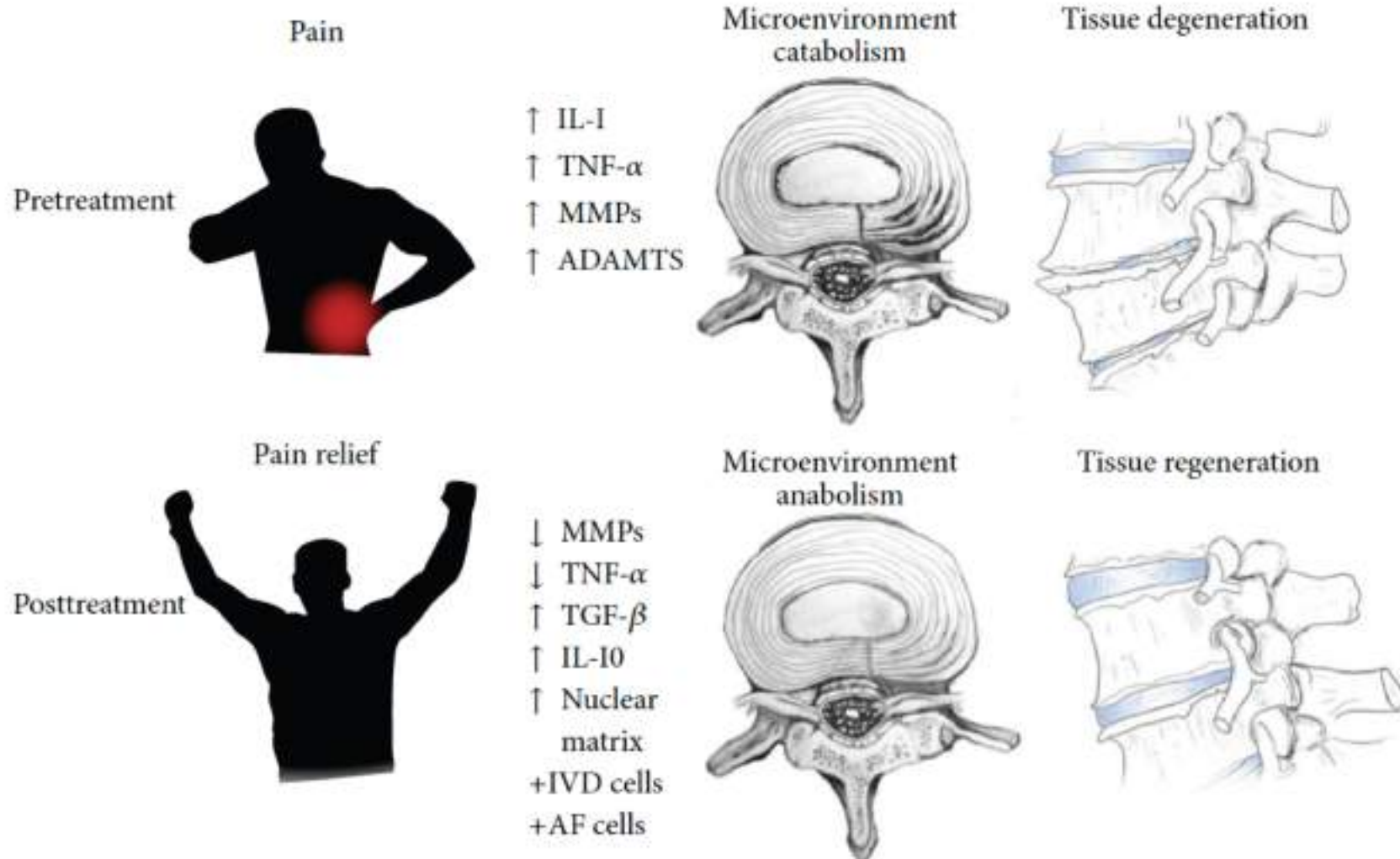
Dégradation du disque IV

- Processus de dégradation
 - Reduction des cellules NP notochorde avec âge --- > diminution anabolisme
 - Epuisement cellulaire + perte de PG/GAG
 - Augmentation médiateurs inflammatoires : IL1, IL6, ICAM1 FGF, NGF
 - Stress oxydatif : AGE, radicaux libres --- > activation NLRP2
 - Cellular senescence, apoptose

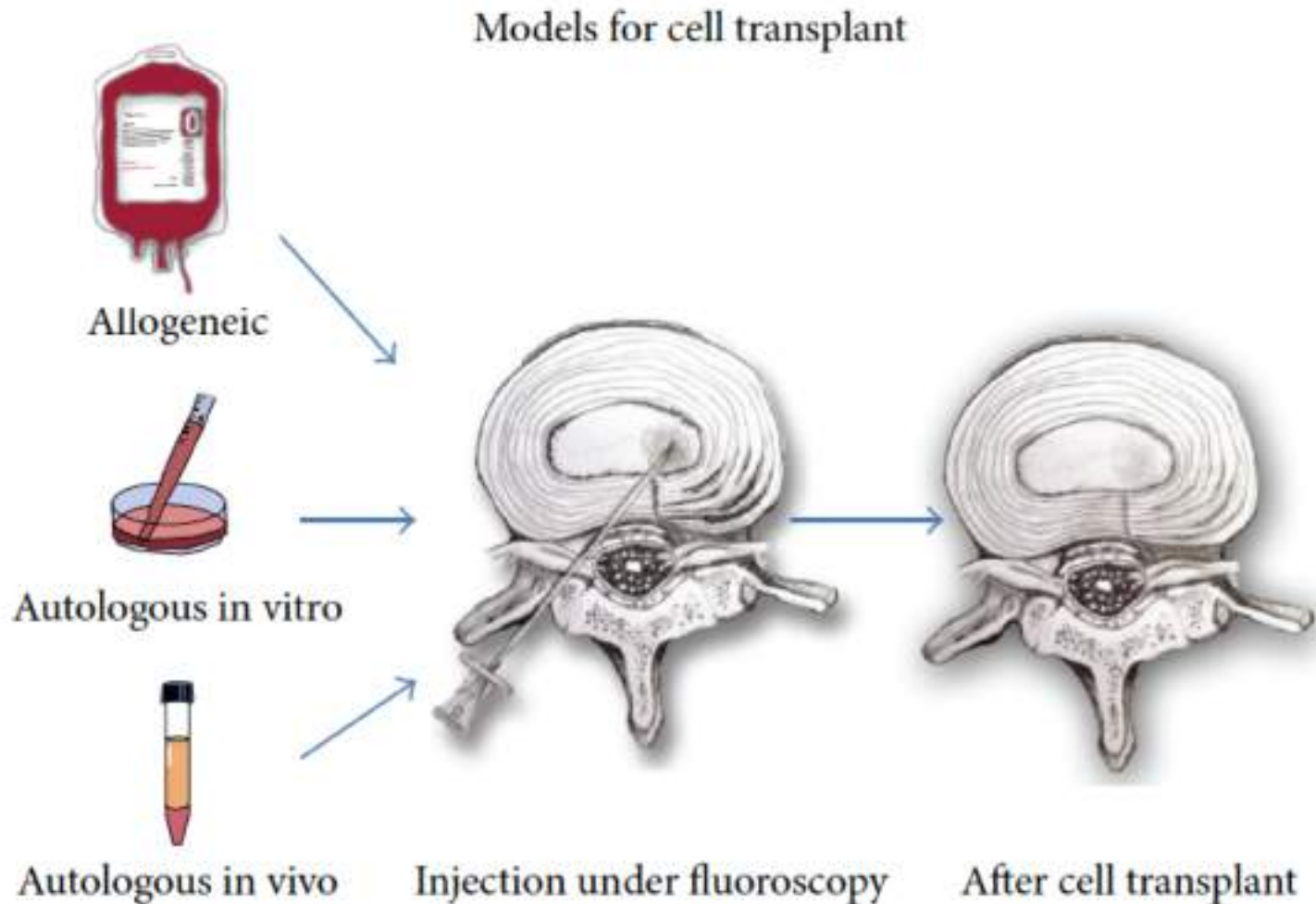


MSC intra-discal injection

Goals of interventional treatment



MSC intra-discal injection

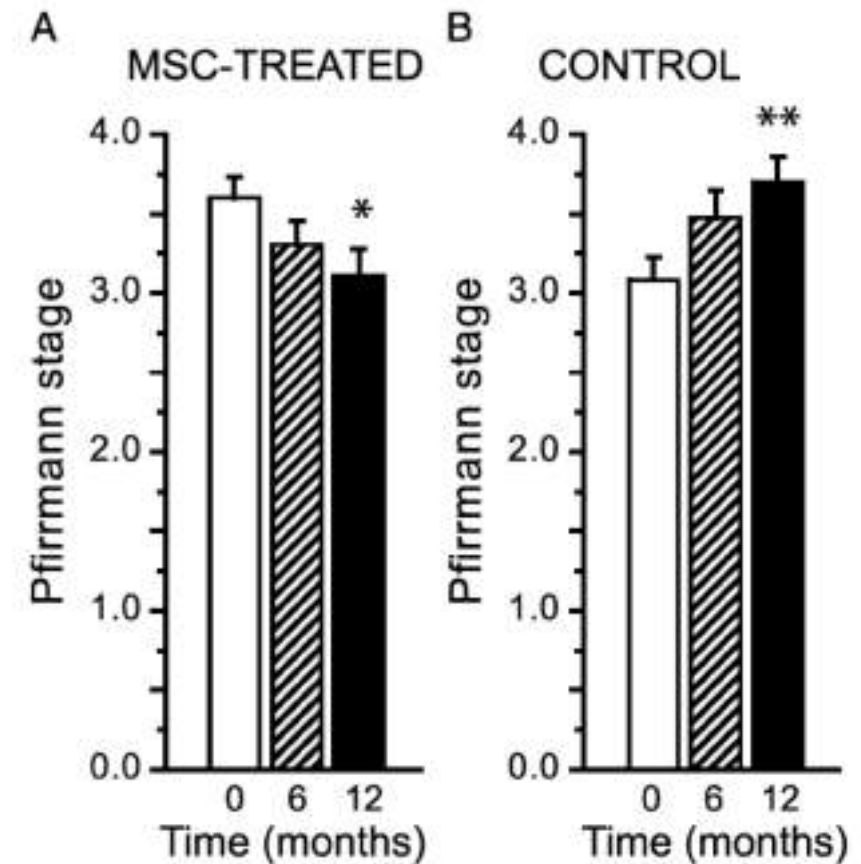
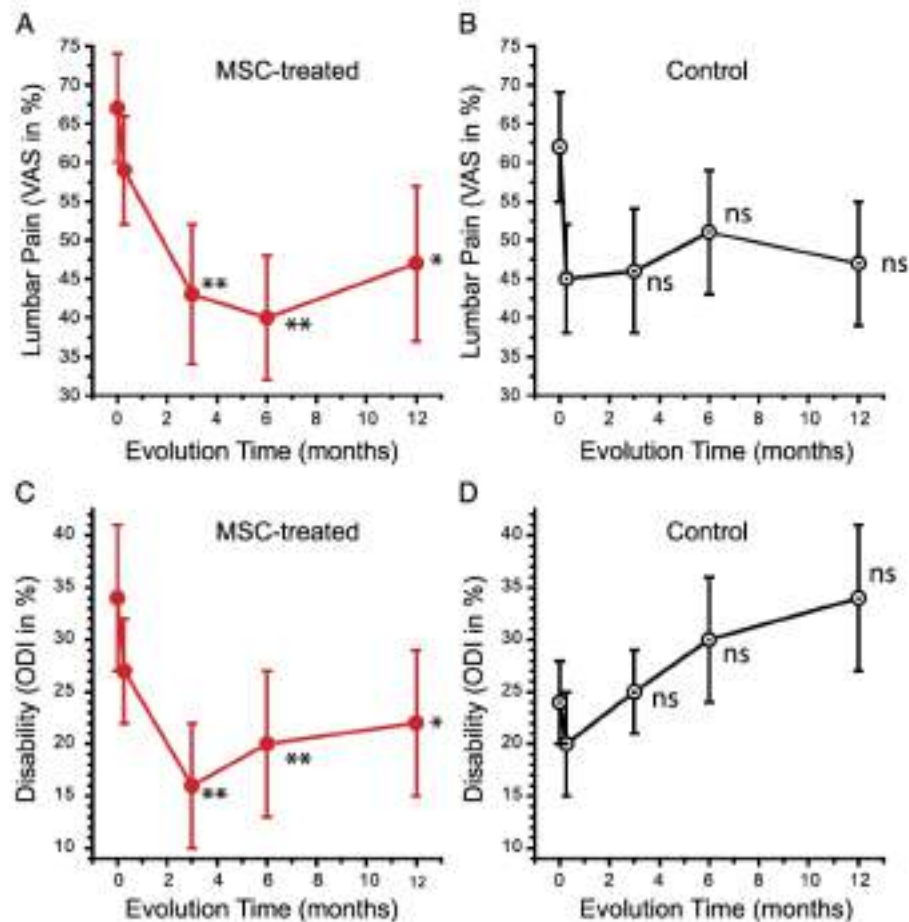


MSC intra-discal injection

- Phase I/II RCT trial with allogeneic BM-MSC
- 24 patients with cLBP
- Intra-discal 25×10^6 vs sham procedure (2 mL)
- MRI stages 2,3 or 4 (Pfirmann)
- 5 donors (viability 98%)

MSC intra-discal injection

- MSC-treated patients displayed a quick and significant improvement in algofunctional indices versus the controls



MSC intra-discal injection

Mesenchymal stem cells can improve discogenic pain in patients with intervertebral disc degeneration: a systematic review and meta-analysis

Wupeng Zhang^{1,2,3†}, Daofeng Wang^{2,3†}, Hua Li^{2,3†}, Gaoxiang Xu^{2,3}, Hao Zhang^{2,3*}, Cheng Xu^{2,3*} and Jiantao Li^{2,3*}

MSC intra-discal injection

TABLE 1 Characteristics of included studies.

Authors	Year	Study design	Sample size (M/C) (n)	VAS	ODI	Reoperation proportion (n)	Fellow up period(y)	AE(n)
Pettine et al	2014	cohort study	26	-	-	2/26	1	0
Noriega et al	2016	RCT	12/12	67 ± 7→	34 ± 7→	0/12	1	0
				47 ± 10	22 ± 10			
Pettine et al	2017	cohort study	26	82.1 ± 2.6→	56.7 ± 3.6→	6/26	3	0
				21.9 ± 4.4	17.5 ± 3.2			
Sairam et al	2022	cohort study	40/40	-	46.1 ± 12.6→	0/40	1	0
					31.1 ± 18.9			
Orozco et al	2011	cohort study	10	68.9 ± 3.3→	25.0 ± 4.1→	0/10	1	0
				20.0 ± 6.5	7.4 ± 2.3			
Kumar et al	2017	cohort study	10	65 ± 12.7→	42.8 ± 15→	0/10	1	0
				29 ± 16.6	16.8 ± 9.8			
Centeno et al	2017	cohort study	33	-	-	2/33	6	0
Pettine et al	2015	cohort study	26	-	-	5/26	2	0
Papadimitriou et al	2021	cohort study	10	-	-	5/10	2	0

M/C, Mesenchymal Stem Cell group/Control group; n, number; RCT, randomized control trial; AE, adverse events; y, year.

MSC intra-discal injection

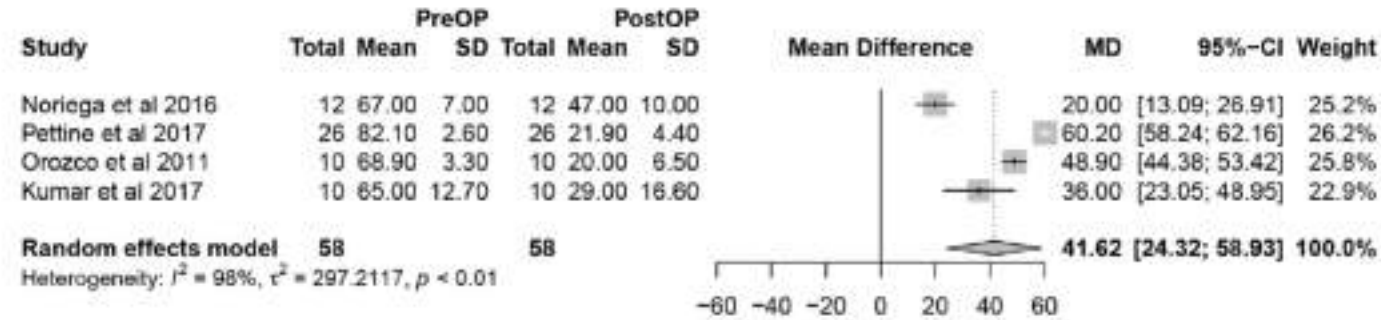


FIGURE 4
Forest plot for the VAS.

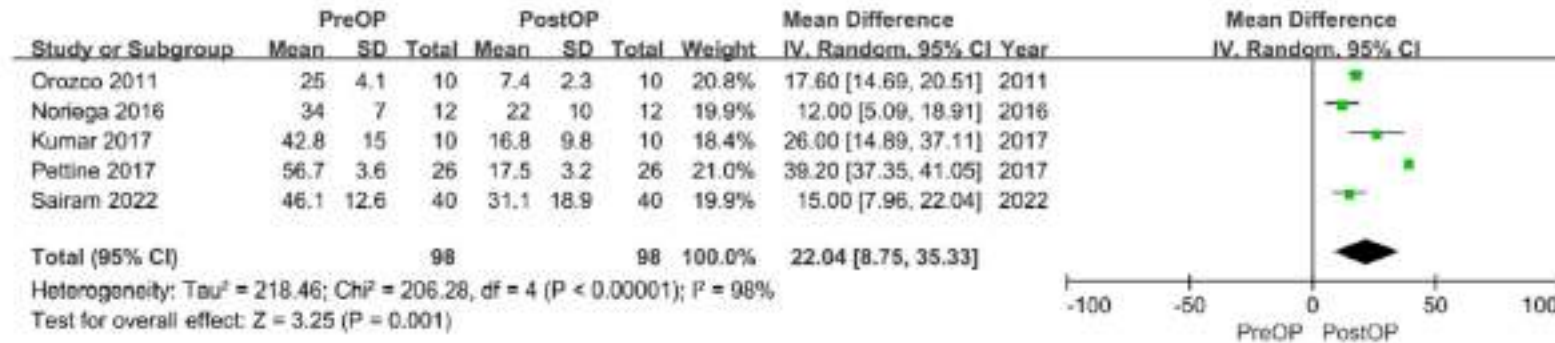
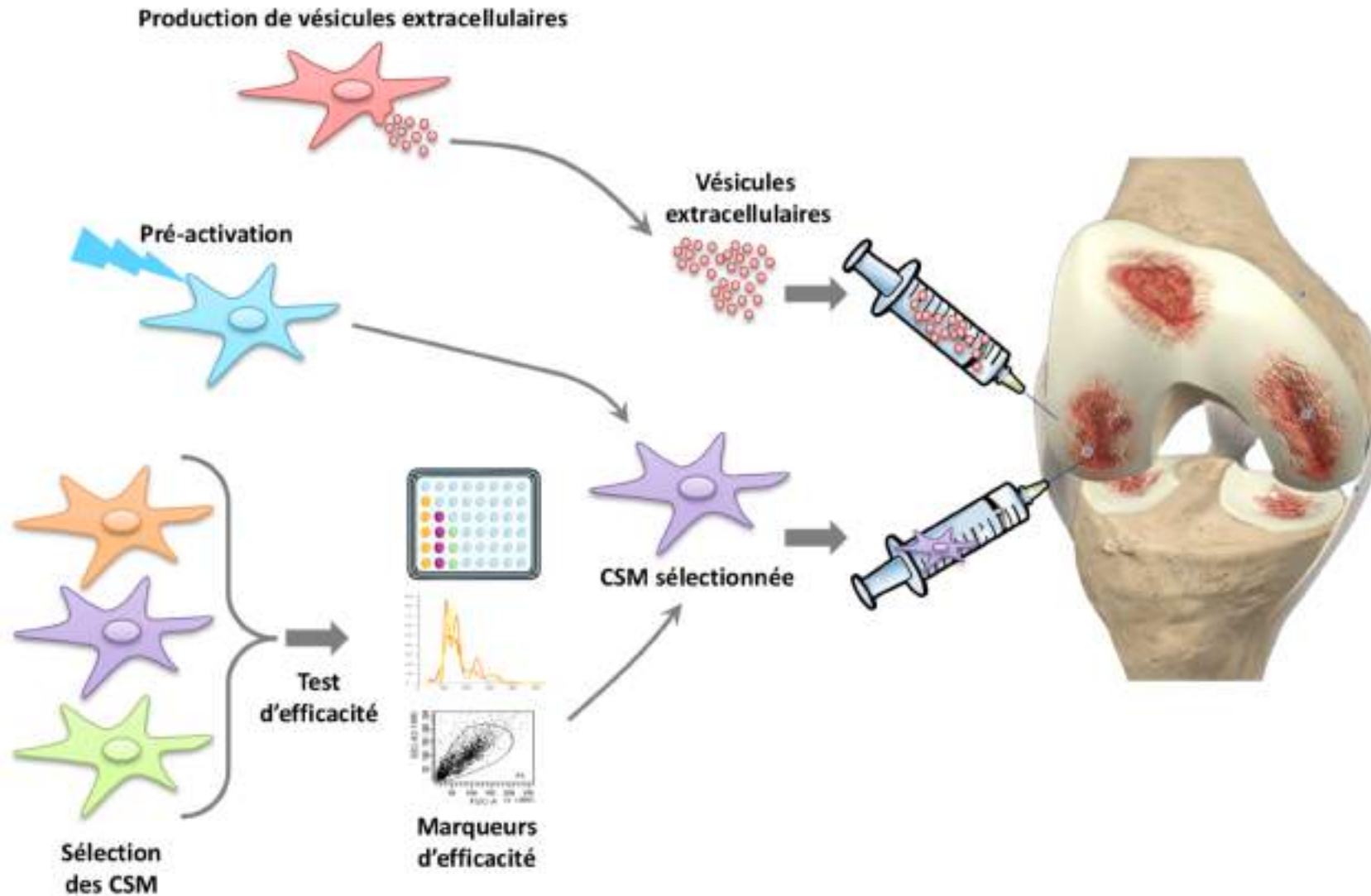


FIGURE 5
Forest plot for the ODI.

Perspectives for MSC therapy



Conclusions : no definitive answer !!!

• We know...

- Positive pre-clinical data
- Numerous published phase I/II
- Excellent tolerance
- Cost issues
- Risk of bias
- Standardisation of cell manufacturing
- Phase II/III negative

• We don't know...

- Tissue repair ?
- Dose ? Frequency of delivery ?
- Type of scaffolds ? 3D printing
- The targeted population ?
- A potency test ? Priming cells ?
- Engineering cell-based approach ?
- Various targeting ?



Limitation = cell integration / indications



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